WEST Search History

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DATE: Thursday, February 03, 2005

search notes

Hide?	Set Name	Query	Hit Count
		DB=USPT; PLUR=YES; OP=AND	
☐	L1	5880141.pn.	1
☐	L2	L1 and (raf or cak or cad or cadtk or pyk or pyk2 or pyk-2 or ca or raftk)	1
☐	L3	$indoline or $indolinone	7886
☐	L4	L3 and (raf or cak or cad or cadtk or pyk or pyk2 or pyk-2 or ca or raftk)	2927
☐	L5	L4 and kinase	243
☐	L6	L5 and tyrosine	174
☐	L7	L5 and $tyrosine	174
☐	L8	modulate or modulator or modulation or regulate or regulator or regulation or inactivate or inactivator or inactivation or agonist or antagonist or inhibit or inhibitor or inhibition or block or blocks or blocking or blocked or blocker	1579503
☐	L9	L8 same l3	396
☐	L10	L9 and l7	84
☐	L11	l10 and pyk2	18
☐	L12	sugen.asn. and (method or process).clm.	98
☐	L13	L12 and l8.clm.	40
☐	L14	L13 not l11	33

END OF SEARCH HISTORY

NiceProt View of Swiss-Prot: Q14289

[Entry info] [Name and origin] [References] [Comments] [Cross-references] [Keywords] [Features] [Sequence] [Tools]

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	**FAK2_HUMAN**
Primary accession number	**Q14289**
Secondary accession numbers	Q13475 Q14290 Q16709
Entered in Swiss-Prot in	Release 36, July 1998
Sequence was last modified in	Release 36, July 1998
Annotations were last modified in	Release 46, February 2005

Name and origin of the protein

Protein name	**Protein tyrosine kinase 2 beta**
Synonyms	**EC 2.7.1.112** **Focal adhesion kinase 2** **FADK 2** **Proline-rich tyrosine kinase 2** **Cell adhesion kinase beta** **CAK beta** **Calcium-dependent tyrosine kinase** **CADTK** **Related adhesion focal tyrosine kinase**
Gene name	**Name: PTK2B** Synonyms: FAK2, PYK2, RAFTK
From	Homo sapiens (Human) [TaxID: 9606]
Taxonomy	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.

References

[1] NUCLEOTIDE SEQUENCE (ISOFORM 1).
TISSUE=Brain;
DOI=10.1038/376737a0;MEDLINE=95379967;PubMed=7544443 [NCBI, ExPASy, EBI, Israel, Japan]
Lev S., Moreno H., Martinez R., Canoll P., Peles E., Musacchio J.M., Plowman G.D., Rudy B., Schlessinger J.;

"Protein tyrosine kinase PYK2 involved in Ca(2+)-induced regulation of ion channel and MAP kinase functions.";
Nature 376:737-745(1995).

[2] NUCLEOTIDE SEQUENCE (ISOFORM 1).
TISSUE=Hippocampus;
DOI=10.1006/geno.1996.0149;MEDLINE=96435932;PubMed=8838818 [NCBI, ExPASy, EBI, Israel, Japan]
Herzog H., Nicholl J., Hort Y.J., Sutherland G.R., Shine J.;
"Molecular cloning and assignment of FAK2, a novel human focal adhesion kinase, to 8p11.2-p22 by nonisotopic in situ hybridization.";
Genomics 32:484-486(1996).

[3] NUCLEOTIDE SEQUENCE (ISOFORM 1).
TISSUE=Hippocampus;
DOI=10.1074/jbc.270.36.21206;MEDLINE=95403356;PubMed=7673154 [NCBI, ExPASy, EBI, Israel, Japan]
Sasaki H., Nagura K., Ishino M., Tobioka H., Kotani K., Sasaki T.;
"Cloning and characterization of cell adhesion kinase beta, a novel protein-tyrosine kinase of the focal adhesion kinase subfamily.";
J. Biol. Chem. 270:21206-21219(1995).

[4] NUCLEOTIDE SEQUENCE (ISOFORM 1).
DOI=10.1074/jbc.270.46.27742;MEDLINE=96070905;PubMed=7499242 [NCBI, ExPASy, EBI, Israel, Japan]
Avraham S., London R., Fu Y., Ota S., Hiregowdara D., Li J., Jiang S., Pasztor L.M., White R.A., Groopman J.E., Avraham H.;
"Identification and characterization of a novel related adhesion focal tyrosine kinase (RAFTK) from megakaryocytes and brain.";
J. Biol. Chem. 270:27742-27751(1995).

[5] NUCLEOTIDE SEQUENCE (ISOFORM 2).
TISSUE=Monocytes;
DOI=10.1074/jbc.273.16.9361;MEDLINE=98211954;PubMed=9545257 [NCBI, ExPASy, EBI, Israel, Japan]
Li X., Hunter D., Morris J., Haskill J.S., Earp H.S.;
"A calcium-dependent tyrosine kinase splice variant in human monocytes. Activation by a two-stage process involving adherence and a subsequent intracellular signal.";
J. Biol. Chem. 273:9361-9364(1998).

[6] NUCLEOTIDE SEQUENCE.
Blechschmidt K., Jandrig B., Baumgart C., Dette M.D., Jahn N., Menzel U., Schilhabel M.B., Wen G., Taudien S., Rosenthal A.;
Submitted (OCT-2000) to the EMBL/GenBank/DDBJ databases.

[7] NUCLEOTIDE SEQUENCE (ISOFORM 1).
TISSUE=Lymph;
DOI=10.1073/pnas.242603899;MEDLINE=22388257;PubMed=12477932 [NCBI, ExPASy, EBI, Israel, Japan]
Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G., Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D., Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K., Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., , Marra M.A.;
"Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences.";
Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).

[8] INTERACTION WITH DDEF2.

PubMed=10022920 [NCBI, ExPASy, EBI, Israel, Japan]
Andreev J., Simon J.-P., Sabatini D.D., Kam J., Plowman G., Randazzo P.A., Schlessinger J.;
"Identification of a new Pyk2 target protein with Arf-GAP activity.";
Mol. Cell. Biol. 19:2338-2350(1999).

[9] PHOSPHORYLATION SITE TYR-402, MUTAGENESIS OF PRO-859, AND INTERACTION WITH NEPHROCYSTIN.
DOI=10.1073/pnas.171269898;MEDLINE=21396557;PubMed=11493697 [NCBI, ExPASy, EBI, Israel, Japan]
Benzing T., Gerke P., Hoepker K., Hildebrandt F., Kim E., Walz G.;
"Nephrocystin interacts with Pyk2, p130(Cas), and tensin and triggers phosphorylation of Pyk2.";
Proc. Natl. Acad. Sci. U.S.A. 98:9784-9789(2001).

[10] PHOSPHORYLATION SITES TYR-579 AND TYR-580.
DOI=10.1073/pnas.2436191100;PubMed=12522270 [NCBI, ExPASy, EBI, Israel, Japan]
Salomon A.R., Ficarro S.B., Brill L.M., Brinker A., Phung Q.T., Ericson C., Sauer K., Brock A., Horn D.M., Schultz P.G., Peters E.C.;
"Profiling of tyrosine phosphorylation pathways in human cells using mass spectrometry.";
Proc. Natl. Acad. Sci. U.S.A. 100:443-448(2003).

Comments

- ***FUNCTION***: Involved in calcium induced regulation of ion channel and activation of the map kinase signaling pathway. May represent an important signaling intermediate between neuropeptide activated receptors or neurotransmitters that increase calcium flux and the downstream signals that regulate neuronal activity. Interacts with the SH2 domain of Grb2. May phosphorylate the voltage-gated potassium channel protein Kv1.2. Its activation is highly correlated with the stimulation of c-Jun N-terminal kinase activity.
- ***CATALYTIC ACTIVITY***: ATP + a protein tyrosine = ADP + a protein tyrosine phosphate.
- ***SUBUNIT***: Interacts with Crk-associated substrate (Cas), PTPNS1 *(By similarity)*, Nephrocystin, DDEF2 and OPHN1L.
- ***SUBCELLULAR LOCATION***: Cytoplasmic. Interaction with Nephrocystin induces the membrane-association of the kinase.
- ***ALTERNATIVE PRODUCTS***:
  - **Alternative splicing [2 named forms] Display all isoform sequences in FASTA format**

    Name 1
    Isoform ID Q14289-1
    This is the isoform sequence displayed in this entry.

    Name 2
    Isoform ID Q14289-2
    Features which should be applied to build the isoform sequence: VSP_004981.

- ***TISSUE SPECIFICITY***: Most abundant in the brain, with highest levels in amygdala and hippocampus. Low levels in kidney. Also expressed in spleen and lymphocytes.
- ***PTM***: Phosphorylated on tyrosine residues in response to various stimuli that elevate the intracellular calcium concentration, as well as by PKC activation. Recruitment by Nephrocystin to cell matrix adhesions initiates Tyr-402 phosphorylation. In monocytes, adherence to substrata is required for tyrosine phosphorylation and kinase activation. Angiotensin II, thapsigargin and L-alpha-lysophosphatidic acid (LPA) also induce autophosphorylation and increase kinase activity *(By similarity)*.
- ***SIMILARITY***: Belongs to the Tyr protein kinase family. FAK subfamily.
- ***SIMILARITY***: Contains 1 FERM domain.

Cross-references

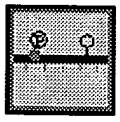
EMBL	U33284; AAC50203.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	L49207; AAB47217.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	D45853; BAA08289.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	U43522; AAC05330.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	S80542; AAB35701.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
	AF311103; -; NOT_ANNOTATED_CDS.	[EMBL / GenBank / DDBJ]
	BC042599; AAH42599.1; -.	[EMBL / GenBank / DDBJ] [CoDingSequence]
PIR	S60248; S60248.	
HSSP	Q05397; 1K04. [HSSP ENTRY / PDB]	
Ensembl	ENSG00000120899; Homo sapiens. [Contig view]	
Genew	HGNC:9612; PTK2B.	
CleanEx	HGNC:9612; PTK2B.	
GeneCards	PTK2B.	
GeneLynx	PTK2B; Homo sapiens.	
GenAtlas	PTK2B.	
MIM	601212 [NCBI / EBI].	
GO	GO:0005737; Cellular component: cytoplasm *(traceable author statement).*	
	GO:0004715; Molecular function: non-membrane spanning protein tyrosine kinase activity *(traceable author statement).*	
	GO:0004871; Molecular function: signal transducer activity *(non-traceable author statement).*	
	GO:0006915; Biological process: apoptosis *(traceable author statement).*	
	GO:0008284; Biological process: positive regulation of cell proliferation *(traceable author statement).*	
	GO:0006468; Biological process: protein amino acid phosphorylation *(traceable author statement).*	
	GO:0006461; Biological process: protein complex assembly *(traceable author statement).*	
	GO:0006950; Biological process: response to stress *(traceable author statement).*	
	GO:0007172; Biological process: signal complex formation *(traceable author statement).*	
	GO:0007165; Biological process: signal transduction *(traceable author statement).*	
	QuickGo view.	
SOURCE	PTK2B; Homo sapiens.	
	IPR000299; Band_4.1.	

InterPro	IPR009065; FERM. IPR005189; Focal_AT. IPR011009; Kinase_like. IPR000719; Prot_kinase. IPR001245; Tyr_pkinase. IPR008266; Tyr_pkinase_AS. Graphical view of domain structure.
Pfam	PF03623; Focal_AT; 1. PF00069; Pkinase; 1. Pfam graphical view of domain structure.
PRINTS	PR00109; TYRKINASE.
ProDom	PD000001; Prot_kinase; 1. [Domain structure / List of seq. sharing at least 1 domain]
SMART	SM00295; B41; 1. SM00219; TyrKc; 1.
PROSITE	PS00660; FERM_1; FALSE_NEG. PS00661; FERM_2; FALSE_NEG. PS50057; FERM_3; 1. PS00107; PROTEIN_KINASE_ATP; 1. PS50011; PROTEIN_KINASE_DOM; 1. PS00109; PROTEIN_KINASE_TYR; 1. PROSITE graphical view of domain structure.
HOVERGEN	[Family / Alignment / Tree]
BLOCKS	Q14289.
ProtoNet	Q14289.
ProtoMap	Q14289.
PRESAGE	Q14289.
DIP	Q14289.
ModBase	Q14289.
SMR	Q14289; 420B21046274E7C2.
SWISS-2DPAGE	Get region on 2D PAGE.
UniRef	View cluster of proteins with at least 50% / 90% identity.

Keywords

Alternative splicing; **ATP-binding**; **Phosphorylation**; **Polymorphism**; **Transferase**; **Tyrosine-protein kinase**.

Features

 Feature table viewer  Feature aligner

Key	From	To	Length	Description	FTId
DOMAIN	39	359	321	FERM.	
DOMAIN	425	683	259	Protein kinase.	
NP_BIND	431	439	9	ATP *(By similarity)*.	
BINDING	457	457		ATP *(By similarity)*.	
ACT_SITE	549	549		Proton acceptor *(By similarity)*.	
DOMAIN	702	767	66	Pro-rich.	

DOMAIN	831	869	39	Pro-rich.	
DOMAIN	868	1009	142	Focal adhesion targeting (FAT).	
MOD_RES	402	402		Phosphotyrosine.	
MOD_RES	579	579		Phosphotyrosine (by autocatalysis).	
MOD_RES	580	580		Phosphotyrosine.	
MOD_RES	881	881		Phosphotyrosine *(By similarity)*.	
VARSPLIC	739	780		Missing (in isoform 2).	VSP_004981
VARIANT	838	838	*	K -> T (in dbSNP:751019) [NCBI/Ensembl].	VAR_020284
MUTAGEN	859	859		P->A: Loss of interaction with nephrocystin.	
CONFLICT	23	23		A -> G (in Ref. 3).	
CONFLICT	256	256		G -> P (in Ref. 2).	
CONFLICT	435	435		F -> L (in Ref. 3).	
CONFLICT	780	780		R -> G (in Ref. 2).	

Sequence information

Length: **1009 AA** Molecular weight: **115875 Da** CRC64: **420B21046274E7C2** [This is a checksum on the sequence]

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MSGVSEPLSR VKLGTLRRPE GPAEPMVVVP VDVEKEDVRI LKVCFYSNSF NPGKNFKLVK

        70         80         90        100        110        120
CTVQTEIREI ITSILLSGRI GPNIRLAECY GLRLKHMKSD EIHWLHPQMT VGEVQDKYEC

       130        140        150        160        170        180
LHVEAEWRYD LQIRYLPEDF MESLKEDRTT LLYFYQQLRN DYMQRYASKV SEGMALQLGC

       190        200        210        220        230        240
LELRRFFKDM PHNALDKKSN FELLEKEVGL DLFFPKQMQE NLKPKQFRKM IQQTFQQYAS

       250        260        270        280        290        300
LREEECVMKF FNTLAGFANI DQETYRCELI QGWNITVDLV IGPKGIRQLT SQDAKPTCLA

       310        320        330        340        350        360
EFKQIRSIRC LPLEEGQAVL QLGIEGAPQA LSIKTSSLAE AENMADLIDG YCRLQGEHQG

       370        380        390        400        410        420
SLIIHPRKDG EKRNSLPQIP MLNLEARRSH LSESCSIESD IYAEIPDETL RRPGGPQYGI

       430        440        450        460        470        480
AREDVVLNRI LGEGFFGEVY EGVYTNHKGE KINVAVKTCK KDCTLDNKEK FMSEAVIMKN

       490        500        510        520        530        540
LDHPHIVKLI GIIEEEPTWI IMELYPYGEL GHYLERNKNS LKVLTLVLYS LQICKAMAYL

       550        560        570        580        590        600
ESINCVHRDI AVRNILVASP ECVKLGDFGL SRYIEDEDYY KASVTRLPIK WMSPESINFR

       610        620        630        640        650        660
RFTTASDVWM FAVCMWEILS FGKQPFFWLE NKDVIGVLEK GDRLPKPDLC PPVLYTLMTR

       670        680        690        700        710        720
CWDYDPSDRP RFTELVCSLS DVYQMEKDIA MEQERNARYR TPKILEPTAF QEPPPKPSRP

       730        740        750        760        770        780
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KYRPPPQTNL LAPKLQFQVP EGLCASSPTL TSPMEYPSPV NSLHTPPLHR HNVFKRHSMR

       790        800        810        820        830        840
EEDFIQPSSR EEAQQLWEAE KVKMRQILDK QQKQMVEDYQ WLRQEEKSLD PMVYMNDKSP

       850        860        870        880        890        900
LTPEKEVGYL EFTGPPQKPP RLGAQSIQPT ANLDRTDDLV YLNVMELVRA VLELKNELCQ

       910        920        930        940        950        960
LPPEGYVVVV KNVGLTLRKL IGSVDDLLPS LPSSSRTEIE GTQKLLNKDL AELINKMRLA

       970        980        990       1000
QQNAVTSLSE ECKRQMLTAS HTLAVDAKNL LDAVDQAKVL ANLAHPPAE
```

Q14289 in FASTA format

View entry in original Swiss-Prot format
View entry in raw text format (no links)
Report form for errors/updates in this Swiss-Prot entry

BLAST submission on ExPASy/SIB or at NCBI (USA)

Sequence analysis tools: ProtParam, ProtScale, Compute pI/Mw, PeptideMass, PeptideCutter, Dotlet (Java)

ScanProsite, MotifScan

Search the SWISS-MODEL Repository

ExPASy Home page	Site Map	Search ExPASy	Contact us	Swiss-Prot

Hosted by NCSC US	Mirror sites:	Australia	Bolivia	Brazil new	Canada	China	Korea	Switzerland	Taiwan

NiceProt View of Swiss-Prot: Q07292

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

Entry name	**KRAF_CAEEL**
Primary accession number	**Q07292**
Secondary accession number	Q9N4E3
Entered in Swiss-Prot in	Release 30, October 1994
Sequence was last modified in	Release 41, February 2003
Annotations were last modified in	Release 46, February 2005

Name and origin of the protein

Protein name	**Raf homolog serine/threonine-protein kinase**
Synonym	**EC 2.7.1.37**
Gene name	**Name: lin-45** Synonyms: raf-1 ORFNames: Y73B6A.5
From	Caenorhabditis elegans [TaxID: 6239]
Taxonomy	Eukaryota; Metazoa; Nematoda; Chromadorea; Rhabditida; Rhabditoidea; Rhabditidae; Peloderinae; Caenorhabditis.

References

[1] NUCLEOTIDE SEQUENCE.
DOI=10.1038/363133a0;MEDLINE=93247635;PubMed=8483497 [NCBI, ExPASy, EBI, Israel, Japan]
Han M., Golden A., Han Y., Sternberg P.W.;
"C. elegans lin-45 raf gene participates in let-60 ras-stimulated vulval differentiation.";
Nature 363:133-140(1993).

[2] NUCLEOTIDE SEQUENCE.
Lee M.-H., Schedl T.;
"Translation repression by GLD-1 protects its mRNA targets from non-sense mediated mRNA decay.";
Submitted (OCT-2003) to the EMBL/GenBank/DDBJ databases.

[3] NUCLEOTIDE SEQUENCE [LARGE SCALE GENOMIC DNA].
STRAIN=Bristol N2;

MEDLINE=99069613;PubMed=9851916 [NCBI, ExPASy, EBI, Israel, Japan]
The C. elegans sequencing consortium;
"Genome sequence of the nematode C. elegans: a platform for investigating biology.";
Science 282:2012-2018(1998).

[4] SEQUENCE REVISION.
WormBase consortium;
Submitted (JUN-2001) to the EMBL/GenBank/DDBJ databases.

Comments

- ***FUNCTION***: Protein kinase that participates in the induction of C.elegans vulva. Acts downstream of the Ras protein let-60.
- ***CATALYTIC ACTIVITY***: ATP + a protein = ADP + a phosphoprotein.
- ***COFACTOR***: Binds 2 zinc ions per subunit *(By similarity)*.
- ***INTERACTION***:
  Q17868:cks-1; NbExp=1; IntAct=EBI-314941, EBI-314859;
  P34766:pal-1; NbExp=1; IntAct=EBI-314941, EBI-311911;
  Q95QC1:r02f2.1; NbExp=1; IntAct=EBI-314941, EBI-331714;
- ***SIMILARITY***: Belongs to the Ser/Thr protein kinase family. RAF subfamily.
- ***SIMILARITY***: Contains 1 Ras-binding (RBD) domain.
- ***SIMILARITY***: Contains 1 zinc-dependent phorbol-ester and DAG binding domain.

Copyright

Cross-references

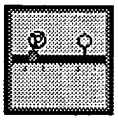
EMBL	L15347; AAA28142.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] AY455928; AAR26307.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] AY493413; AAR86712.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence] AC024204; AAF36042.1; -. [EMBL / GenBank / DDBJ] [CoDingSequence]
PIR	S33261; S33261.
HSSP	P35968; 1VR2. [HSSP ENTRY / PDB]
IntAct	Q07292; -.
Ensembl	Y73B6A.5; Caenorhabditis elegans. [Contig view]
WormBase	WBGene00003030; Y73B6A.5.
WormPep	Y73B6A.5; CE25585. [WormPep / WorfDB]
InterPro	IPR002219; DAG_PE-bind. IPR011009; Kinase_like. IPR000719; Prot_kinase. IPR003116; RBD. IPR008271; Ser_thr_pkin_AS. Graphical view of domain structure.
Pfam	PF00130; DAG_PE-bind; 1. PF00069; Pkinase; 1. PF02196; RBD; 1. Pfam graphical view of domain structure.
PRINTS	PR00008; DAGPEDOMAIN.
ProDom	PD000001; Prot_kinase; 1. [Domain structure / List of seq. sharing at least 1 domain]
SMART	SM00109; C1; 1.

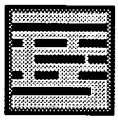
	SM00455; RBD; 1.
PROSITE	PS00479; DAG_PE_BIND_DOM_1; 1. PS50081; DAG_PE_BIND_DOM_2; 1. PS00107; PROTEIN_KINASE_ATP; 1. PS50011; PROTEIN_KINASE_DOM; 1. PS00108; PROTEIN_KINASE_ST; 1. PS50898; RBD; 1. PROSITE graphical view of domain structure.
BLOCKS	Q07292.
ProtoNet	Q07292.
ProtoMap	Q07292.
PRESAGE	Q07292.
DIP	Q07292.
ModBase	Q07292.
SMR	Q07292; 6376E968D11A9E49.
SWISS-2DPAGE	Get region on 2D PAGE.
UniRef	View cluster of proteins with at least 50% / 90% identity.

Keywords

ATP-binding; **Metal-binding**; **Phorbol-ester binding**; **Serine/threonine-protein kinase**; **Transferase**; **Zinc**.

Features

 Feature table viewer

 Feature aligner

Key	From	To	Length	Description
DOMAIN	85	161	77	Ras-binding.
DOMAIN	171	217	47	Phorbol-ester and DAG binding.
DOMAIN	481	748	268	Protein kinase.
NP_BIND	487	495	9	ATP *(By similarity)*.
METAL	184	184		Zinc 2 *(By similarity)*.
METAL	187	187		Zinc 2 *(By similarity)*.
METAL	198	198		Zinc 1 *(By similarity)*.
METAL	201	201		Zinc 1 *(By similarity)*.
METAL	206	206		Zinc 2 *(By similarity)*.
METAL	209	209		Zinc 2 *(By similarity)*.
METAL	217	217		Zinc 1 *(By similarity)*.
BINDING	507	507		ATP *(By similarity)*.
ACT_SITE	602	602		Proton acceptor *(By similarity)*.
CONFLICT	801	801		A -> R (in Ref. 1).

Sequence information

Length: **813** **AA** Molecular weight: **90407** **Da** CRC64: **6376E968D11A9E49** [This is a checksum on the sequence]

```
        10         20         30         40         50         60
MSRINFKKSS ASTTPTSPHC PSPRLISLPR CASSSIDRKD QASPMASPST PLYPKHSDSL

        70         80         90        100        110        120
HSLSGHHSAG GAGTSDKEPP KFKYKMIMVH LPFDQHSRVE VRPGETARDA ISKLLKKRNI
```

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       130        140        150        160        170        180
TPQLCHVNAS SDPKQESIEL SLTMEEIASR LPGNELWVHS EYLNTVSSIK HAIVRRTFIP

       190        200        210        220        230        240
PKSCDVCNNP IWMMGFRCEF CQFKFHQRCS SFAPLYCDLL QSVPKNEDLV KELFGIASQV

       250        260        270        280        290        300
EGPDRSVAEI VLANLAPTSG QSPAATPDSS HPDLTSIKRT GGVKRHPMAV SPQNETSQLS

       310        320        330        340        350        360
PSGPYPRDRS SSAPNINAIN DEATVQHNQR ILDALEAQRL EEESRDKTGS LLSTQARHRP

       370        380        390        400        410        420
HFQSGHILSG ARMNRLHPLV DCTPLGSNSP SSTCSSPPGG LIGQPTLGQS PNVSGSTTSS

       430        440        450        460        470        480
LVAAHLHTLP LTPPQSAPPQ KISPGFFRNR SRSPGERLDA QRPRPPQKPH HEDWEILPNE

       490        500        510        520        530        540
FIIQYKVGSG SFGTVYRGEF FGTVAIKKLN VVDPTPSQMA AFKNEVAVLK KTRHLNVLLF

       550        560        570        580        590        600
MGWVREPEIA IITQWCEGSS LYRHIHVQEP RVEFEMGAII DILKQVSLGM NYLHSKNIIH

       610        620        630        640        650        660
RDLKTNNIFL MDDMSTVKIG DFGLATVKTK WTVNGGQQQQ QPTGSILWMA PEVIRMQDDN

       670        680        690        700        710        720
PYTPQSDVYS FGICMYEILS SHLPYSNINN RDQILFMVGR GYLRPDRSKI RHDTPKSMLK

       730        740        750        760        770        780
LYDNCIMFDR NERPVFGEVL ERLRDIILPK LTRSQSAPNV LHLDSQYSVM DAVMRSQMLS

       790        800        810
WSYIPPATAK TPQSAAAAAA ANKKAYYNVY GLI
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5. A method for the modulation of the catalytic activity of a protein kinase comprising contacting said protein kinase with a compound, salt or prodrug of claim 1.

6. The method of claim 5 wherein said protein kinase comprises a protein tyrosine kinase.

7. The method of claim 6 wherein said protein tyrosine kinase comprises a receptor tyrosine kinase.

8. The method of claim 7 wherein said receptor tyrosine kinase is selected from from the group consisting of EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR.alpha., PDGFR.beta., CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.

9. The method of claim 5 wherein said protein tyrosine kinase comprises a cellular tyrosine kinase.

10. The method of claim 9 wherein said non-receptor protein tyrosine kinase is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

11. The method of claim 5 wherein said protein kinase comprises a serine-threonine protein kinase.

12. The method of claim 11 wherein said serine-threonine protein kinase is selected from the group consisting of CDK2 and Raf.

13. A method for the modulation of the catalytic activity of a protein kinase comprising contacting said protein kinase with said compound, salt or prodrug of claim 1.

14. The method of claim 13 wherein said protein kinase comprises a protein tyrosine kinase.

15. The method of claim 14 wherein said protein tyrosine kinase comprises a receptor protein tyrosine kinase.

16. The method of claim 15 wherein said receptor protein tyrosine kinase is selected from the group consisting of EGF, HER2, HER3, HER4, IR, IGF-LR, IRR, PDGFR.alpha., PDGFR.beta., CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.

17. The method of claim 14 wherein said protein tyrosine kinase comprises a non-receptor protein tyrosine kinase.

18. The method of claim 17 wherein said non-receptor protein tyrosine kinase is is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

19. The method of claim 13 wherein said protein kinase comprises a serine-threonine protein kinase.

20. The method of claim 12 wherein said serine-threo

13. A method for the modulation of the catalytic activity of a protein kinase, comprising contacting said protein kinase with a compound or salt of claim 1.

14. The method of claim 13, wherein said protein kinase comprises a receptor protein tyrosine kinase.

15. The method of claim 14, wherein said receptor protein tyrosine kinase is selected from the group consisting of EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR.alpha., PDGFR.beta., CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R.

16. The method of claim 13, wherein said protein kinase comprises a non-receptor protein tyrosine kinase.

17. The method of claim 16, wherein said non-receptor protein tyrosine kinase is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes/Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

18. The method of claim 13, wherein said protein kinase comprises a serine-threonine protein kinase.

19. The method of claim 18, wherein said serine-threonine protein kinase is selected from the group consisting of CDK2 and Raf.

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Tyrosine phosphorylation modulates the activity of clostridial neurotoxins.

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Clostridial neurotoxins' metalloprotease domain selectively cleaves proteins implicated in the process of synaptic vesicle fusion with the plasma membrane and, accordingly, blocks neurotransmitter release into the synaptic cleft. Here we investigate the potential modulation of these neurotoxins by intracellular cascades triggered by environmental signals, which in turn may alter its activity on target substrates. We report that the nonreceptor tyrosine kinase Src phosphorylates botulinum neurotoxins A, B, and E and tetanus neurotoxin. Protein tyrosine phosphorylation of serotypes A and E dramatically increases both their catalytic activity and thermal stability, while dephosphorylation reverses the effect. This suggests that the biologically significant form of the neurotoxins inside neurons is phosphorylated. Indeed, in PC12 cells in which tyrosine kinases such as Src and **PYK2** are highly abundant, stimulation by membrane depolarization in presence of extracellular calcium induces rapid and selective tyrosine phosphorylation of internalized light chain, the metalloprotease domain, of botulinum toxin A. These findings provide a conceptual framework to connect intracellular signaling pathways involving tyrosine kinases, G-proteins, phosphoinositides, and calcium with the action of botulinum neurotoxins in abrogating vesicle fusion and neurosecretion.

Tags: In Vitro; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

Descriptors: *Botulinum Toxins--metabolism--ME; *Botulinum Toxins --pharmacology--PD; *Membrane Proteins; *Neurotoxins--metabolism--ME; *Neurotoxins--pharmacology--PD; *Tyrosine--metabolism--ME; Animals; Kinetics; Metalloendopeptidases--metabolism--ME; Mice; Nerve Tissue Proteins--metabolism--ME; PC12 Cells; Phosphorylation; Protein-Tyrosine Kinase--metabolism--ME; Rats; Signal Transduction; Substrate Specificity; Synaptic Transmission--drug effects--DE; Synaptic Vesicles--drug effects --DE; src-Family Kinases--metabolism--ME

CAS Registry No.: 0 (Botulinum Toxins); 0 (Membrane Proteins); 0 (Nerve Tissue Proteins); 0 (Neurotoxins); 0 (synaptosomal-associated protein 25); 55520-40-6 (Tyrosine)

Enzyme No.: EC 2.7.1.- (protein tyrosine kinase **PYK2**); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.112 (src-Family Kinases); EC 3.4.24 (Metalloendopeptidases)

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L14: Entry 21 of 33 File: USPT May 23, 2000

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TITLE: Method and compositions for treatment of BCR-ABL associated leukemias and other cell proliferative disorders

DATE-ISSUED: May 23, 2000

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/7.23; 435/7.1, 435/7.2, 435/7.24, 436/63, 436/64

CLAIMS:

What is claimed is:

1. A method for identifying a compound to be tested for an ability to modulate a cell proliferative disorder involving a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex comprising:

(a) contacting a cell that forms a complex comprising a GRB-2 adaptor polypeptide SH2- or SH3-binding portion of the protein tyrosine kinase polypeptide and an SH2 or SH3 portion of the GRB-2 adaptor polypeptide with the the compound for a time sufficient to allow intracellular binding of the compound to the complex or at least one of the polypeptides;

(b) detecting the level of the complex present in the cell of step (a); and

(c) comparing the level of the complex detected in step (b) to the level of complex present in a cell of the type in step (a) that has not contacted the compound, so that if the level detected in step (b) is less than the level present in a cell that has not been contacted with the compound, a compound to be tested for an ability to modulate a cell proliferative disorder involving a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex is identified.

2. The method of claim 1 wherein the protein tyrosine kinase polypeptide of the the protein tyrosine kinase/GRB-2 adaptor polypeptide complex is a transmembrane, receptor protein tyrosine kinase polypeptide.

3. The method of claim 1 wherein the protein tyrosine kinase polypeptide of the the protein tyrosine kinase/GRB-2 adaptor polypeptide complex is an intracellular, cytoplasmic protein tyrosine kinase polypeptide.

4. The method of claim 3 wherein the intracellular, cytoplasmic protein

tyrosine kinase polypeptide of the protein tyrosine kinase/GRB-2 adaptor polypeptide complex is a BCR-ABL intracellular, cytoplasmic protein tyrosine kinase polypeptide.

5. The method of claim 1 wherein the protein tyrosine kinase polypeptide of the the protein tyrosine kinase/GRB-2 adaptor polypeptide complex is an intracellular, nuclear protein tyrosine kinase polypeptide.

6. The method of claim 1 wherein the GRB-2 adaptor polypeptide SH2- or SH3-binding portion of the protein tyrosine kinase polypeptide comprises at least 1 phosphorylated tyrosine amino acid residue.

7. The method of claim 1 wherein the GRB-2 adaptor polypeptide SH2- or SH3-binding portion of the protein tyrosine kinase polypeptide comprises a phosphorylation domain.

8. The method of claim 1 wherein the GRB-2 adaptor polypeptide SH2- or SH3-binding portion of the protein tyrosine kinase polypeptide comprises at least 4 consecutive amino acid residues of an SH2-binding domain.

9. The method of claim 1 wherein the GRB-2 adaptor polypeptide SH2- or SH3-binding portion of the protein tyrosine kinase polypeptide comprises an SH3-binding domain.

10. The method of claim 9 wherein the SH3-binding domain is at least 4 amino acid residues in length.

11. The method of claim 9 wherein the SH3-binding domain is at least 10 amino acids in length.

12. The method of claim 1 wherein the compound identified disrupts a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex.

13. The method of claim 1 wherein the compound identified modulates a cell proliferative disorder involving a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex.

14. The method of claim 13 wherein the compound identified disrupts a BCR/ABL polypeptide/GRB-2 adaptor polypeptide complex.

15. The method of claim 14 wherein the compound identified modulates a cell proliferative disorder involving a BCR/ABL polypeptide/GRB-2 adaptor polypeptide complex.

16. The method of claim 15 wherein the cell proliferative disorder is a chronic chronic myelogenous leukemia.

17. The method of claim 15 wherein the cell proliferative disorder is an acute lymphocytic leukemia.

18. The method of claim 15 wherein the cell proliferative disorder is an acute myelogenous leukemia.

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United States Patent [19]

Schlessinger et al.

[11] Patent Number: 6,066,463

[45] Date of Patent: May 23, 2000

[54] **METHOD AND COMPOSITIONS FOR TREATMENT OF BCR-ABL ASSOCIATED LEUKEMIAS AND OTHER CELL PROLIFERATIVE DISORDERS**

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[73] Assignees: **New York University**, New York, N.Y.; **Duke University**, Durham, N.C.; **Sugen, Inc.**, South San Francisco, Calif.

[21] Appl. No.: **08/246,441**

[22] Filed: **May 20, 1994**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/127,922, Sep. 28, 1993, abandoned.

[51] **Int. Cl.**[7] **G01N 33/574**; G01N 33/53; G01N 33/48

[52] **U.S. Cl.** **435/7.23**; 435/7.24; 435/7.2; 435/7.1; 436/63; 436/64

[58] **Field of Search** 435/7.23, 7.24; 424/9.2, 138.1; 436/63, 64

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(List continued on next page.)

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[57] **ABSTRACT**

The present invention relates to compositions and methods for the prevention and treatment of cell proliferative disorders wherein a protein tyrosine kinase or protein tyrosine phosphatase capable of complexing with a member of the SH2- and/or SH3-containing family of adaptor proteins is involved. This invention is based, in part, on the surprising discovery that the adaptor protein, GRB-2, binds the intracellular BCR-ABL tyrosine kinase product in vivo and is necessary for the activation of the oncogenic potential of the BCR/ABL product. The present invention further relates to protein tyrosine kinase/adaptor protein complexes and the uses of these complexes for the identification of agents capable of decreasing or inhibiting the interaction between the members of such complexes.

18 Claims, 20 Drawing Sheets